Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative

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Background Although intravenous morphine is commonly used for the treatment of chest pain in patients presenting with non–ST-segment elevation acute coronary syndromes (NSTE ACS), its safety has not been evaluated. The CRUSADE Initiative is a nonrandomized, retrospective, observational registry enrolling patients with NSTE ACS to evaluate acute medications and interventions, inhospital outcomes, and discharge treatments.

Methods The study population comprised patients presenting with NSTE ACS at 443 hospitals across the United States from January 2001 through June 2003 (n = 57,039). Outcomes were evaluated in patients receiving morphine versus not and between patients treated with morphine versus intravenous nitroglycerin.

Results A total of 17,003 patients (29.8%) received morphine within 24 hours of presentation. Patients treated with any morphine had a higher adjusted risk of death (odds ratio [OR] 1.48, 95% CI 1.33-1.64) than patients not treated with morphine. Relative to those receiving nitroglycerin, patients treated with morphine also had a higher adjusted likelihood of death (OR 1.50, 95% CI 1.26-1.78). Utilizing a propensity score matching method, the use of morphine was associated with increased inhospital mortality (OR 1.41, 95% CI 1.26-1.57). The increased risk of death in patients receiving morphine persisted across all measured subgroups.

Conclusions Use of morphine either alone or in combination with nitroglycerin for patients presenting with NSTE ACS was associated with higher mortality even after risk adjustment and matching on propensity score for treatment. This analysis raises concerns regarding the safety of using morphine in patients with NSTE ACS and emphasizes the need for a randomized trial. (Am Heart J 2005;149:1043-9.)

See related Editorial on page 945.

The care of acute myocardial infarction and acute coronary syndromes has certainly progressed since Sir James MacKenzie suggested treating cardiac patients with bed rest, morphine and chloroform until unconsciousness ensued.[1] The current American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction—collectively known as non–ST-segment elevation acute coronary syndromes (NSTE ACS)—continue to recommend intravenous (IV) morphine as a class IC indication for patients with suspected acute coronary syndromes whose pain is not relieved after nitroglycerin or whose symptoms recur. However, there have never been any randomized, controlled, clinical trials or large-scale observations evaluating the efficacy or safety of morphine in this population, so this recommendation is based solely upon expert consensus, not upon clinical trial evidence.[2] Given the lack of data regarding the use of IV morphine for patients presenting with acute coronary syndromes, we evaluated the use of morphine within the first 24 hours after presentation in patients from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) Quality Improvement Initiative.

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Methods

Patients

Patients entered in the CRUSADE database from January 2001 through June 2003 were evaluated for this analysis. CRUSADE is a multidisciplinary quality improvement initiative for acute coronary syndrome patients across 443 emergency departments and medical centers. Patients included in the CRUSADE Initiative have ischemic symptoms at rest within 24 hours prior to presentation and high-risk features including ST-segment depression ≥0.5 mm, transient ST-segment elevation 0.5-1.0 mm (lasting for <10 min), and/or positive cardiac markers (elevated troponin I or T and/or creatine-kinase [CK]-MB > upper limit of normal [ULN] for the local laboratory assay).

Data were collected only during the initial hospitalization in an anonymous fashion and the institutional review board of each institution approved participation in this initiative. Data collected included use of acute medications within 24 hours of presentation, use and timing of invasive cardiac procedures, laboratory results, clinical outcomes, and discharge therapies and interventions. Contraindications to therapies given Class IA or IB recommendations by the ACC/AHA guidelines were recorded.[2] We excluded patients who were transferred out to another institution, because data could not be collected after transfer due to current United States privacy regulations. We first sought to compare patients who received IV morphine versus those who did not receive IV morphine. However, morphine is often used for treatment of ongoing chest pain symptoms or congestive heart failure (both high-risk features). IV nitroglycerin, though, represents an alternative therapy for unstable patients with such symptoms. Additionally, the impact of IV nitroglycerin has been evaluated by large, randomized, clinical trials and found to have a neutral effect on mortality or other acute clinical events. As such, in a secondary analysis, we compared patients who received IV nitroglycerin only to (1) patients who received IV morphine only and (2) patients who received both IV nitroglycerin and IV morphine.

End points

Inhospital outcomes including inhospital death, recurrent myocardial infarction, congestive heart failure, and cardiogenic shock were reported by sites and were not adjudicated by an independent clinical events committee. Recurrent infarction was defined as a new ischemic event thought by the site to be unrelated to the initial presenting ischemic event. For events occurring before revascularization procedures, ischemic symptoms had to be accompanied by new Q waves on the electrocardiogram in ≥2 contiguous leads and/or be associated with re-elevation of the local laboratory CK-MB or troponin (> ULN if cardiac markers before the event were normal or >50% of the most recent cardiac marker result if CK-MB or troponin were > ULN prior to the new event). For recurrent infarction events associated with revascularization procedures, the same electrocardiographic criteria applied. For cardiac marker analyses in this setting, CK-MB levels had to be >50% of the most recent cardiac marker result if CK-MB levels were > ULN prior to percutaneous coronary intervention (PCI) or CK-MB levels post-PCI had to be >3 times ULN if the most recent CK-MB level was normal. The same criteria applied for CK-MB analyses post-coronary artery bypass graft (CABG) surgery except that CK-MB levels post-CABG had to be >5 times ULN if the most recent CK-MB level was normal.

Statistical analysis

Patient characteristics, care patterns, and inhospital clinical outcomes were compared across all groups. Medians with 25th and 75th percentiles were reported for continuous variables and frequencies for categorical variables. Kruskal-Wallis (>2 comparison groups) and Wilcoxon rank-sum (2 comparison groups only) tests were used for continuous variables and χ^2 tests were used for categorical variables.

Because CRUSADE is an observational study, patients were not randomized by treatment. For the first set of the multivariate analyses, we compared patients who received IV morphine to those who did not receive IV morphine with respect to outcomes (eg, post-admission infarction, cardiogenic shock, congestive heart failure, death, and the composite outcome of post-admission infarction or death). For these analyses, generalized estimating equations were used to adjust for correlations among clustered responses (eg, within hospital correlations)[3] because patients within a single hospital are more likely to be similar. Additional generalized estimating equations were performed by decomposing IV morphine use into within- and among-center components, resulting 2 odds ratio estimates but focused on within-center component for interpretation. In addition, these models adjusted for baseline patient clinical risk factors including age, sex, body mass index, race, family history of coronary artery disease, hypertension, diabetes, smoking status, hypercholesterolemia, prior myocardial infarction, prior PCI, prior CABG, prior congestive heart failure, prior stroke, renal insufficiency, ST-segment depression, transient ST-segment elevation, positive cardiac markers, sign of congestive heart failure, heart rate, systolic blood pressure, and insurance status as well as for provider and hospital characteristics (physician specialty, total number of hospital beds, region of the country, presence of cardiac catheterization, coronary intervention and bypass surgery facilities, and type of hospital—academic or nonacademic).

For the second and third sets of analyses, we focused the comparison on patients who received IV morphine versus IV nitroglycerin only, and both IV morphine and IV nitroglycerin, where the comparator was those patients who received IV nitroglycerin only. Similar risk-adjusted analyses were performed as in the overall morphine analysis.

As an additional way of accounting for nonrandom treatment assignment, we adjusted for factors favoring selection of one treatment over another using propensity scores.[4,5] Using multivariable generalized estimating equations, a propensity score model was created to estimate the likelihood of IV morphine treatment. For the first approach, the total study population was then stratified into quintiles of equal size based on the estimated propensity scores. Within each quintile, the comparison of IV morphine and inhospital mortality was examined using the χ^2 test. For the second approach (propensity score matched pairs method), the individual probability of receiving IV morphine was matched for patients who received IV morphine and patients who did not receive IV morphine. Lastly, subgroup analyses were performed to further explore the effects of IV morphine on inhospital mortality.

Table I. Baseline characteristics and acute (<24 hours) treatments by morphine use

Patient characteristics*	Overall (n = 57,039)	No morphine (n = 40,036)	Morphine (n = 17,003)	*P*
Baseline characteristics				
Age (y)†	68 (56, 79)	70 (58, 79)	65 (54, 76)	<.0001
Male sex	59.4	58.4	61.8	<.0001
History of CAD	35.6	34.6	38.0	<.0001
Hypertension	68.9	69.7	67.2	<.0001
Diabetes mellitus	32.6	33.0	31.5	.0004
Smoking	27.2	24.8	32.9	<.0001
Hyperlipidemia	46.4	46.0	47.3	.009
Prior MI	31.1	30.5	32.6	<.0001
Prior PCI	21.6	20.6	23.9	<.0001
Prior CABG	20.4	20.3	20.7	.4
Prior CHF	18.8	19.3	17.7	<.0001
Renal insufficiency	13.8	14.3	12.7	<.0001
Admission signs/symptoms				
ST depression	40.0	39.1	42.1	<.0001
Transient ST elevation	10.2	9.0	12.9	<.0001
Positive cardiac markers	87.9	87.2	89.4	<.0001
Signs of CHF	22.5	22.7	22.1	.1
Heart rate (beats/min)†	82 (70, 98)	83 (70, 98)	81 (69, 97)	<.0001
Systolic BP (mm Hg)†	144 (124, 165)	144 (124, 165)	144 (123, 164)	.4
Acute medications				
Aspirin	91.2	90.9	91.9	.0002
All heparin	82.2	79.7	87.8	<.0001
β-Blocker	78.1	77.2	80.1	<.0001
Clopidogrel	40.0	38.1	44.5	<.0001
GP IIb/IIIa inhibitor	35.2	30.6	45.7	<.0001
Inhospital procedures				
Diagnostic cath	66.1	62.9	73.7	<.0001
PCI	36.5	33.6	43.2	<.0001
CABG	11.5	11.2	12.2	.001

CAD, Coronary artery disease; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *CHF*, congestive heart failure; *BP*, blood pressure; *GP*, glycoprotein; *cath*, catheterization.
*Data are presented as percentages unless otherwise indicated.
†Presented as median (25th, 75th percentiles).

Table II. Clinical events by morphine use

Outcomes	No morphine (n = 40,036)	Morphine (n = 17,003)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Death	4.7%	5.5%	1.22 (1.10-1.34)	1.48 (1.33-1.64)
Death or MI	7.1%	8.5%	1.26 (1.17-1.35)	1.44 (1.34-1.56)
Post-admission MI	3.0%	3.8%	1.28 (1.17-1.41)	1.34 (1.22-1.48)
Cardiogenic shock	2.3%	3.8%	1.63 (1.45-1.82)	1.71 (1.53-1.91)
CHF	9.1%	10.3%	1.16 (1.09-1.24)	1.27 (1.19-1.36)

OR, Odds ratio; *MI*, myocardial infarction; *CHF*, congestive heart failure.

A *P* value of <.05 was established as the level of statistical significance for all tests. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

Results

Morphine versus no morphine: Baseline characteristics and treatment

In this cohort of 57,039 high-risk patients with NSTE ACS, 17,003 (29·8%) patients were treated with morphine within the first 24 hours following hospital presentation. Patients who received morphine had higher incidences of ST-segment depression, transient ST-segment elevation, and positive cardiac markers (Table I).

Patients who received morphine were more likely to receive evidence-based medications and treatments than were patients who did not receive morphine. Patients receiving morphine were also more likely to have an electrocardiogram performed within 10 minutes of arrival (38.4% vs 30.5%, $P < .0001$), to be cared for by a

Table III. Inhospital mortality in quintiles of patients grouped by propensity to receive morphine

Outcomes	No morphine	morphine	Adjusted OR (95% CI)*
Quintile 1 (lowest propensity to receive morphine)	7.0%	11.0%	1.64 (1.41-1.92)
Quintile 2	5.4%	7.8%	1.48 (1.25-1.74)
Quintile 3	4.4%	5.8%	1.34 (1.12-1.60)
Quintile 4	3.3%	4.5%	1.36 (1.11-1.66)
Quintile 5 (highest propensity to receive morphine)	2.2%	2.5%	1.14 (0.89-1.46)

OR, Odds ratio.
*No morphine versus IV morphine alone.

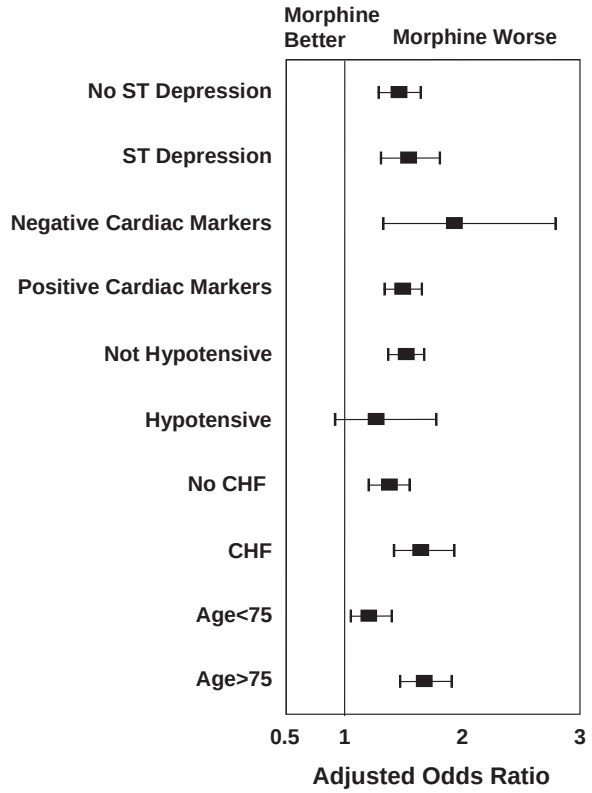
cardiologist 64.8% vs 55.9%, $P < .0001$), and to undergo invasive cardiac procedures (Table I).

Morphine versus no morphine: Association with inhospital outcomes

Unadjusted and adjusted rates of adverse clinical outcomes were higher in patients who received IV morphine compared with those who did not (Table II). The rate of myocardial infarction increased from 3.0% to 3.8%, death increased from 4.7% to 5.5%, and the composite end point of death or myocardial infarction increased from 7.1% to 8.5%. After adjustment, the rates of all measured end points, including myocardial infarction (adjusted odds ratio [OR] 1.34, 95% CI 1.22-1.48), death (adjusted OR 1.48, 95% CI 1.33-1.64), and the composite end point of death or MI (adjusted OR 1.44, 95% CI 1.34-1.56), remained significantly higher in patients who received IV morphine. The results were similar after adjusting for within- and among-center variations, as there was no indication that centers with a higher percentage of morphine use provided worse care.

Propensity score analysis was performed to further evaluate the effects of IV morphine on inhospital mortality. Characteristics most strongly associated with receiving morphine included age, transient ST-segment elevation, ST-segment depression, positive cardiac markers, and being cared for by a cardiologist. In the propensity score matched pairs analysis (including 33,972 patients), baseline characteristics for patients who received IV morphine versus those who did not receive morphine were similar except for the incidence of ST-segment depression (42.1% vs 40.5%, respectively, $P = .003$). From the matched pairs propensity score, the use of morphine was associated with increased inhospital mortality (odds ratio 1.41, 95% CI 1.26-1.57). The patients who did and did not receive morphine were also divided into quintiles by propensity to receive morphine. In each quintile, with the exception of the fifth quintile (highest propensity to receive morphine), patients who received morphine experienced higher inhospital mortality (Table III).

Figure 1



Adjusted odds ratios of inhospital mortality with IV morphine use by subgroups. *CHF*, Congestive heart failure.

Additionally, we evaluated the risk of IV morphine administration in several specific subgroups. The increased risk of death in patients who received IV morphine was consistent across all measured subgroups (Figure 1).

Morphine versus IV nitroglycerin

We also examined the patients who received IV nitroglycerin. The baseline characteristics of the patients were similar. Compared to patients receiving only IV nitroglycerin, patients who received IV morphine alone were less likely to receive evidence-based medications and treatments. The patients who received morphine alone were also less likely to be cared for by a cardiologist (56.2% vs 65.8%, $P < .0001$) or to receive an electrocardiogram within 10 minutes of arrival (34.0% vs 35.8%, $P < .02$) (Table IV). Clinical events and odds ratios as stratified by administration of IV morphine and nitroglycerin are shown in Table V.

Table IV. Baseline characteristics and acute (<24 hours) treatments by morphine and nitroglycerin use

Patient characteristics*	IV NTG only (n = 13,217)	IV Morphine only (n = 7189)	P
Baseline characteristics			
Age (y)†	68 (56, 78)	67 (55, 78)	.004
Male sex	60.7	58.1	.0002
History of CAD	37.5	37.0	.5
Hypertension	69.3	66.9	.0003
Diabetes mellitus	31.8	32.4	.4
Smoking	27.9	30.6	<.0001
Hyperlipidemia	49.5	43.7	<.0001
Prior MI	31.6	32.3	.4
Prior PCI	23.6	21.1	<.0001
Prior CABG	21.3	19.2	.0005
Prior CHF	15.8	20.8	<.0001
Renal insufficiency	12.5	14.4	<.0001
Admission signs/ symptoms			
ST depression	42.5	39.6	<.0001
Transient ST elevation	11.2	11.5	.4
Positive cardiac markers	89.4	88.3	.02
Signs of CHF	21.1	25.1	<.0001
Heart rate (beats/min)†	81 (69, 97)	83 (70, 100)	<.0001
Systolic BP (mm Hg)†	147 (128, 169)	142 (121, 162)	<.0001
Acute medications			
Aspirin	92.5	90.3	<.0001
All heparin	90.4	81.7	<.0001
β-Blocker	80.7	76.4	<.0001
Clopidogrel	45.1	38.3	<.0001
GP IIb/IIIa inhibitor	43.7	34.9	<.0001
Inhospital procedures			
Diagnostic cath	75.8	64.5	<.0001
PCI	44.5	34.5	<.0001
CABG	14.1	9.9	<.0001

IV, Intravenous; *NTG*, nitroglycerin; *CAD*, coronary artery disease; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *CHF*, congestive heart failure; *BP*, blood pressure; *GP*, glycoprotein; *cath*, catheterization.
*Data presented as percentages unless otherwise indicated.
†Presented as median (25th, 75th percentiles).

Compared with patients who received IV nitroglycerin alone, morphine-only patients had significantly increased unadjusted and adjusted risks of adverse clinical outcomes.

We next compared patients who received both IV nitroglycerin and IV morphine (n = 9814) to patients receiving IV nitroglycerin only. Patients receiving both IV nitroglycerin and morphine had slightly higher incidences of ST-segment depression, transient ST-segment elevation, and positive cardiac markers than did the nitroglycerin-only patients. When compared to the patients who received only IV nitroglycerin, patients receiving combination therapy also were more likely to receive evidence-based medications and therapies than were patients receiving nitroglycerin alone. When the combination therapy patients were compared to the nitroglycerin-only group, we found that the patients who received morphine in addition to nitroglycerin were at significantly increased risk for all measured end points, including death (adjusted OR 1.41, 95% CI 1.21-1.64), post-admission MI (adjusted OR 1.31, 95% CI 1.14-1.51), death or MI (adjusted OR 1.34, 95% CI 1.19-1.50), cardiogenic shock (adjusted OR 1.49, 95% CI 1.27-1.74), and congestive heart failure (adjusted OR 1.28, 95%CI 1.17-1.41).

Table V. Clinical outcomes by morphine and nitroglycerin use

Outcomes	IV NTG only (n = 13,217)	IV morphine only (n = 7189)	Adjusted OR (95% CI)*
Death	3.8%	6.8%	1.49 (1.25-1.77)
Post-admission MI	3.2%	3.5%	1.18 (0.99-1.41)
Death or MI	6.5%	9.6%	1.40 (1.22-1.62)
Cardiogenic shock	2.4%	4.0%	1.44 (1.19-1.74)
CHF	8.8%	10.5%	1.06 (0.93-1.20)

IV, Intravenous; *NTG*, nitroglycerin; *OR*, odds ratio; *MI*, myocardial infarction; *CHF*, congestive heart failure.
*IV NTG alone versus IV morphine alone.

Discussion

We evaluated >57,000 patients presenting to US hospitals with NSTE ACS and demonstrated that patients treated with morphine had a higher risk of death and other adverse clinical outcomes even though these patients were more likely to be treated with evidence-based medications and to undergo invasive cardiac procedures. These findings persisted even when we controlled for the concomitant use of IV nitroglycerin (which may designate higher risk patients with ongoing ischemic symptoms and signs of congestive heart failure) and adjusted for differences in baseline characteristics. Additionally, we found that the higher risk of mortality remained present after evaluation by matched-pairs propensity analysis. This increase in mortality was consistent across all measured subgroups.

Several possibilities exist as to why patients who received IV morphine had a higher risk of adverse outcomes. First, morphine may be a marker for suboptimal medical care. However, our analysis found that patients who received IV morphine were significantly more likely to receive other acute evidence-based therapies, including aspirin, β-blockers, heparin, clopidogrel, and glycoprotein IIb/IIIa inhibitors. Additionally, the patients who received morphine were also more likely to be cared for by a cardiologist and to undergo

invasive cardiac procedures. Thus, it does not seem likely that the increased mortality in patients receiving morphine is due to substandard medical care.

Second, morphine use may simply be a marker for sicker patients, such as those with ongoing chest pain or with congestive heart failure, because morphine is a widely used treatment for both of these conditions.[2] However, patients who received IV morphine were no more likely to exhibit signs of congestive heart failure at presentation than patients who did not receive the therapy. Additionally, by comparing morphine recipients to patients who received IV nitroglycerin, we were able to further evaluate the subgroup of patients who would have required continued treatment for chest pain. In doing so, we found that patients who received only IV nitroglycerin had better outcomes than patients who received IV morphine. Additionally, we found that patients who received combination therapy also had worse outcomes than patients who received solely IV nitroglycerin. Furthermore, it is possible that some of the association of early morphine use on mortality may be due to its use in palliative or pre-terminal care. We therefore performed further sensitivity analyses after excluding all deaths within 24 hours (n = 149). These analyses did not differ significantly from the previously described analyses that did not exclude early deaths. Thus it does not seem likely that the worse outcomes seen in patients receiving IV morphine can be attributed to higher early acuity in these patients.

Third, the well-described analgesic effects of IV morphine may serve to blunt the severity of angina without actually ameliorating the underlying pathophysiologic cause of chest pain (ie, coronary hypoperfusion). Finally, IV morphine may actually be deleterious to patients with NSTE ACS. Rather than simply masking the pain associated with myocardial ischemia, perhaps morphine actually exacerbates the crisis. Morphine has several well known and potentially harmful side effects. Most commonly, morphine causes hypotension, bradycardia and respiratory depression.[6-10] These deleterious effects can result in decreased myocardial oxygen delivery, decreased arterial oxygenation, increase in arterial carbon dioxide, and perhaps even cerebral hypoperfusion.[11,12] In one study of patients with coronary artery disease awaiting bypass surgery, morphine caused a 13% reduction in coronary blood flow.[13] In fact, in animal studies, morphine has been demonstrated quite conclusively to actually increase myocardial infarction size.[14] These side effects could well result in deleterious outcomes in patients with acute coronary syndromes who might lack the coronary reserve required to withstand the stresses of hypotension and hypoxemia.

Notwithstanding the findings of this study, there are several limitations to our analysis. First, this was not a randomized clinical trial, so unmeasured treatment biases that could not be controlled for with multivariate and propensity analyses may have influenced the results. Second, the dosing and exact timing of morphine and nitroglycerin use were not collected, so we could not determine how these variables influenced the results of the analysis and how patients' clinical statuses changed acutely as a result of using these medications. Additionally, we could not adequately account for differences in rates of medication use and procedure utilization between analysis groups, so residual confounding may be present. Finally, nonfatal clinical outcomes were not centrally adjudicated, so the results might have been different if clinical outcomes were rigorously defined.

The first use of morphine to relieve chest pain in acute myocardial infarction was documented in the medical literature in 1912,[15] and subsequently, IV morphine has been commonly used as an acute anti-anginal therapy for almost a century. Ironically, several studies suggest that morphine is not the most efficacious agent in the relief of chest pain,[16-18] but the ACC/AHA guidelines for patients with unstable angina and non–ST-segment elevation myocardial infarction give intravenous morphine a class IC recommendation for patients presenting with acute coronary syndromes who have continued chest pain because there have been no prospective studies evaluating the use of morphine for this indication. Given the adverse outcomes associated with IV morphine use in this analysis, a prospective, randomized, clinical trial is needed to determine whether morphine should be administered to patients with chest pain and acute coronary syndromes.

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